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Effect of Rivastigmine on Mobility of Patients with Higher-Level Gait Disorder: A Pilot Exploratory Study

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Abstract

Background Higher-level gait disorder (HLGD) in older adults is characterized by postural instability, stepping dysrhythmicity, recurrent falls and progressive immobility. Cognitive impairments are frequently associated with HLGD.

Objectives The aim of this study was to compare gait and cognitive performance before and after the use of rivastigmine in patients with HLGD, free from cognitive impairment or Parkinsonism.

Methods Fifteen non-demented patients with HLGD (age 79.2 ± 5.9 years; 11 women; Mini-Mental State

Examination [MMSE] 28.3 ± 1.4) received escalating doses of rivastigmine for 12 weeks in an open-label, pilot study. They were assessed before and after treatment (week 0 and week 12), and after a 4-week washout period (week 16). Assessments included the Mindstreams computerized neuropsychological battery, Activities-specific Balance Confidence Scale, State-Trait Anxiety Inventory, Geriatric Depression Scale, Timed Up and Go (TUG) test, gait speed and stride time variability. One-way multiple analysis of variance tests for repeated measures were used, and Pillai's trace test was considered as robust to investigate significant differences.

Results The mean dose of rivastigmine during the 8–12 week period was 5.1 ± 2.3 mg/day. A positive effect was observed on the Mindstreams memory subscale and anxiety scores [Pillai's trace: $F(6,724) = 0.508$, $p = 0.010$; and $F(7,792) = 0.545$, $p = 0.006$, respectively, over the course of the study] as well as on mobility (TUG test) [Pillai's trace: $F(4,863) = 0.448$; $p = 0.028$], whereas gait speed and stride time variability did not change.

Conclusions The use of relatively low-dose rivastigmine did not affect gait speed and stride time variability; however, the general mobility and anxiety were improved. These preliminary results warrant a larger, randomized, placebo-controlled study.

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1 Introduction

Higher-level gait disorder (HLGD) is a progressive multifactorial disorder in elderly adults, characterized by slow gait, stepping dysrhythmicity, postural instability, recurrent falls, progressive immobility, wheelchair use and institutionalization [1–5]. The pathophysiology of gait and balance impairment in people with HLGD is poorly

understood and cannot be explained by motor, sensory, pyramidal, extrapyramidal, cerebellar, autonomic or peripheral disturbances [2].

Cognitive functions play an important role in the regulation of walking, particularly in older adults where deficits in executive functions and attention are independently associated with postural instability, impairments in daily living activities, and falls [6, 7]. In support of this idea, acetylcholinesterase inhibitors, cognitive enhancer medications for symptomatic treatment of patients with Alzheimer's and Parkinson's diseases, were found to reduce gait variability [8], and increase gait velocity [9, 10], in patients with Alzheimer's disease [9, 10], and to reduce fall risks in patients with Alzheimer's disease and in non-demented patients with Parkinson's disease [9, 10].

Two additional, randomized controlled, double-blind trials examining the effect of cholinesterase inhibitors on gait in a larger cohort of individuals with mild cognitive impairment [11] and in non-demented patients with Parkinson's disease are currently recruiting patients [12]. The aim of this study was to evaluate the effect of rivastigmine, an inhibitor of both butyrylcholinesterase and acetylcholinesterase, on locomotion and cognitive functions in elderly patients with HLGD who are free from cognitive or other motor impairments in an open-label, pilot exploratory study. Cholinergic agents affect many aspects of cognition, which suggests that the primary effect may be on an attention or executive system with a secondary modulating influence on memory, language, and visuospatial skills; improvement in attention may further reduce apathy. Cholinesterase inhibitors may play an important role in controlling neuropsychiatric and behavioral disturbances in patients, i.e. depression, anxiety, disinhibition and agitation [13]. The midbrain mesencephalic locomotor region (MLR), comprising the pedunculopontine (PPN) and cuneiform nuclei (CN) [14], has recently been highlighted as an important region with respect to gait and balance disorders [15, 16].

On the basis of these data, together with the fact that specific lesions of the cholinergic PPN neurons in monkeys induce gait and postural deficits [17], we hypothesized that cholinergic deficit may contribute to the gait and balance disorders presented by HLGD patients, and that cholinesterase inhibitors could improve balance and reduce falls in subjects with HLGD.

2 Methods

2.1 Subjects

Twenty consecutive consenting patients with HLGD (14 women, age range 69–89 years, mean 79.6 ± 6.1 years)

who attended our Movement Disorders Unit were originally enrolled in this pre-post intervention study. These patients were diagnosed as having HLGD by three movement disorders specialists (NG, TG and DM) using criteria described previously [2]. Any other causes for their gait difficulties were excluded in the clinical evaluation. All 20 subjects were able to walk independently for at least 30 m. Those who were on a stable dose of other medications for at least 1 month prior to the baseline assessment agreed not to change their medications during the 16 weeks of the current study. Patients diagnosed as having dementia according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria and Mini-Mental State Examination (MMSE) scores less than 26 were excluded, as were those with clinically significant depression, orthopedic problems and any other neurological abnormalities that could have had an effect on gait and postural responses. Patients with a history of severe head trauma or stroke and those with significant structural brain lesions on computerized tomography or with clinically significant orthostatic hypotension were also excluded. In addition, we excluded patients with active malignancy, uncontrolled symptomatic heart disease, diabetes mellitus or hypertension, as well as those with psychiatric disorders. All of the enrolled patients had normal vitamin B₁₂, folic acid, as well as general hematology, electrolytes, renal and liver function tests, and a negative venereal disease research laboratory (VDRL) test. The study was approved by the Ethics Committee of the Tel Aviv Medical Center, and each patient signed an informed consent form prior to enrolling in the study.

2.2 Drug Escalation

Rivastigmine was given orally at an initial dose of 1.5 mg twice daily. This dose was increased to 3 mg twice daily after 4 weeks, and to 4.5 mg twice daily after 8 weeks. Patients who developed side effects at any stage were either left on the same dose for 2 or more weeks or had their daily dose reduced to the previous level. We tried to keep the dose of rivastigmine constant at the maximal tolerated dose between week 8 and week 12 of the trial, the point at which administration of the drug was stopped.

2.3 Clinical Evaluations

The patients were assessed at baseline (week 0), shortly after the termination of rivastigmine medication (week 12), and after a 4-week washout period (week 16). Each assessment included evaluation of the subject's general condition together with registration of vital functions and side effects. Also included were the scores of the MMSE [18], the short form of the Geriatric Depression Scale

(GDS) [19], the Activities-specific Balance Confidence scale (ABC) for measuring the level of fear of falling [20], and the State-Trait Anxiety Inventory (STAI) [21]. Cognitive performance was assessed using Mindstreams, a computerized neuropsychological battery, which includes tests for the domains of memory, attention, executive, visual-spatial functions and global cognitive function [22]. All cognitive scores in Mindstreams are normalized, where 100 is the mean and one SD is 15 points for matched age and education levels (we therefore used cutoff scores <85 to denote impairment).

2.4 Gait Assessment

The Timed Up and Go (TUG) test [23] was administered for a general assessment of balance, mobility, lower extremity function, and fall risk [24, 25]. A computerized force-sensitive system was used to quantify gait and stride-to-stride variability [26]. The system measures the forces underneath the foot as a function of time and consists of a pair of insoles (footswitch) and a recording unit. Each insole contains four load sensors that cover the surface of the sole and measure the normal (vertical) forces under the foot. A small recording unit ($11.5 \times 6.5 \times 3.5$ cm; 0.5 kg) is carried on the subject's waist. Plantar pressures under each foot are recorded at a rate of 100 Hz. Measurements are stored in a memory card during the walk, after which they are transferred to a personal computer for further analysis. Average stride time and stride time variability were determined from the recorded force using previously described methods [27, 28]. Variability measures were quantified by means of the coefficient of variation, e.g. stride-time variability = $100 \times (\text{average stride time}/\text{standard deviation})$.

2.5 Statistics

The descriptive step included a calculation of mean and standard deviation. All numeric variables were analyzed using repeated measures. One-way multiple analysis of variance (MANOVA) was used to compare the three assessments on weeks 0, 12, and 16. In all cases, the post hoc Pillai's trace test was considered as robust to investigate significant differences. The results were evaluated in a confidence interval range of 95 % and a significance level of $p < 0.05$. Statistical analysis was performed using SPSS statistical software (SPSS, Chicago, IL, USA).

3 Results

The 20 enrolled patients had suffered from gait disorders for 3.9 ± 3.6 years before enrolling in the study. Three

patients dropped out at weeks 3–4 into the study due to general weakness, fatigue, insomnia and/or non-compliance while on a dose of 1.5 mg twice daily. Two patients stopped escalation of rivastigmine at 3–4 weeks, while on a stable dose of 3.0 mg, because of dizziness, vertigo, nausea, blurred vision, diarrhea, general weakness and/or fatigue, which completely disappeared following dose lowering. Fifteen patients (mean age 79.2 ± 5.9 years, range 72–89 years, 11 women) completed the study. The mean rivastigmine dose at study closure (week 12) was 5.1 ± 2.3 mg (range 3.0–9.0 mg). The effects of rivastigmine on mental functions, affect and gait are presented in Table 1.

The mean Mindstreams memory subscale scores consistently improved, from 85.7 ± 9.6 at baseline to 88.97 ± 6.6 at week 12, and further to 93.9 ± 13.1 at week 16 [Pillai's trace $F(6,724) = 0.508$; $p = 0.010$]. The size effect of rivastigmine on the memory subscale was considerable, exceeding 10 points, in 12 patients (80 %).

The mean anxiety scores according to the STAI scale improved from 37.5 ± 7.6 points at baseline to 34.3 ± 8.1 points at the end of the medication period (week 12), returning to 38.5 ± 10 points after washout (week 16) [Pillai's trace $F(7,792) = 0.545$; $p = 0.006$].

Locomotion and mobility significantly improved according to the TUG test, changing from 14.1 ± 3.8 s at baseline to 13.1 ± 2.4 s at week 12 and 13.5 ± 2.5 s at week 16, indicating a significant beneficial drug effect [Pillai's trace $F(4,863) = 0.448$; $p = 0.028$]. In contrast, rivastigmine treatment had no effect on MMSE, ABC and GDS scores, and other (non-memory) Mindstreams domains, as well as on gait speed and stride-time variability (Table 1).

4 Discussion

HLGD is a disease of old age resulting in restriction of mobility and often accompanied by cognitive decline [29]. The association between cognitive decline and mobility impairments in the elderly is now well established [30], and abnormal gait itself is an early marker for future cognitive decline [31]. The present pilot study was an open-labeled exploratory trial that suggested a possible positive rivastigmine effect on cognitive and motor function. The benefits of rivastigmine, if confirmed in future studies, can be attributed to its effect on affect (anxiety) and/or cognition (executive functions). Decrease of the anxiety level with rivastigmine treatment has also been reported in patients with Alzheimer's disease [32].

Rivastigmine's treatment association with shortening of the TUG test may be indicative of improved mobility, stability, and decrease in fall risk in patients with HLGD.

Table 1 Effects of rivastigmine on cognitive characteristics and gait parameters in 15 patients with higher-level gait disorder

	Baseline, week 0 (<i>n</i> = 15)	After treatment, week 12 (<i>n</i> = 15)	Washout after treatment, week 16 (<i>n</i> = 15)	Pillai's trace test
Mean rivastigmine dose (mg/day)	0	5.1 ± 2.3	0	
MMSE	28.3 ± 1.4	28.13 ± 1.1	28.4 ± 1.4	NS
Mindstreams global cognitive score	90.43 ± 7.1	91.52 ± 7.5	93.47 ± 9.8	NS
Memory subscale	85.75 ± 9.6	88.97 ± 6.6	93.98 ± 13.1	$F(6,724) = 0.508$; $p = 0.010$
Anxiety subscale	37.46 ± 7.6	34.26 ± 8.1	38.53 ± 10.0	NS
Executive function subscale	90.10 ± 8.5	90.56 ± 8.4	92.72 ± 8.7	NS
Visuospatial subscale	86.49 ± 11.0	86.99 ± 15.8	86.6 ± 12.7	NS
Attention subscale	92.48 ± 14.9	96.29 ± 12.7	98.19 ± 12.8	NS
ABC (fear of falling) scale	68.3 ± 12.6	69.7 ± 16.0	65.7 ± 17.8	NS
STAI (Spielberger Anxiety Inventory)	37.5 ± 7.6	34.3 ± 8.1	38.5 ± 10	$F(7,792) = 0.545$; $p = 0.006$
Geriatric Depression Scale	9.4 ± 5.7	9.07 ± 5.3	10.26 ± 5.8	NS
Timed Up and Go test (s)	14.1 ± 3.8	13.1 ± 2.4	13.5 ± 2.5	$F(4,863) = 0.448$; $p = 0.028$
Gait speed (m/s)	0.86 ± 0.8	0.90 ± 0.1	0.90 ± 0.2	NS
Stride-time variability (%)	3.65 ± 1.3	3.29 ± 1.0	3.36 ± 1.3	NS

MMSE Mini-Mental State Examination, NS not significant, ABC Activities-specific Balance Confidence scale, STAI State-Trait Anxiety Inventory

^a *F* indicates variance analysis of repeated measurements

The TUG test requires a transfer from sitting to standing, walking and turning, and is influenced by walking speed, muscle strength and balance [33, 34]. The TUG test is a sensitive and specific measure for identifying community-dwelling adults who are at risk for falls [35]. Time to completion above 14 s indicates a high risk of falls in the elderly population [25, 36].

Timing of the TUG test also reflects cognitive abilities, given its independent association with better performance on global cognition, memory tests and faster processing speed in community-dwelling adults older than 50 years of age [37]. Earlier studies reported that rivastigmine had significantly improved executive function on tests for flexibility of thinking, problem solving and planning in patients with parkinsonian dementia [38, 39]. Our results have not demonstrated an effect on executive functions, probably because of a ceiling effect. The same explanation probably applies to the lack of effect on MMSE, attention and visuospatial skills. These findings support the hypothesis that rivastigmine may affect frontal subcortical circuits in parkinsonian patients [39], although we did not observe any improvement of executive functions in the present study. The limited effect of rivastigmine on gait that had been observed in the present study may have been caused by the comparatively low doses of the medicament. Nevertheless, it was accompanied by considerable adverse effects. Advanced patch delivery transdermal systems

containing larger doses of rivastigmine may be more effective because of the stable rivastigmine plasma levels and better tolerability [40].

Limitations of this study include the small number of participants, making the power of this study low, and its open-label design (allowing training or a placebo effect on mobility as well as on anxiety).

Although we did not employ a blinded evaluator, it ought to be outlined that the present study included mainly the Mindstreams computerized tests as an endpoint, and that the target kinematic measures were generated automatically. Placebo-controlled studies with larger doses of rivastigmine are needed to determine the possibility of further improvements of locomotion and better performance of activities of daily living in elderly individuals with HLGD.

5 Conclusions

The findings of this exploratory, small, open-label study indicate a possible positive effect of rivastigmine on anxiety and mobility in patients with HLGD. The possibility that the drug will have the capability to prevent falls and maintain independent mobility justifies a large-scale, placebo-controlled clinical trial with a calculation of a theoretical number needed to show a result in advance.

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